PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference L/2BJ18/JV/1	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/011953	International filing date *(day/month/year)* 20.10.2004	Priority date *(day/month/year)* 20.10.2003
International Patent Classification (IPC) or national classification and IPC A61K51/04, A61K51/08, A61P35/00		
Applicant UNIVERSITÄT ZÜRICH et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of Invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.12.2005	27.02.2006
Name and mailing address of the International preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Gonzalez Ramon, N Telephone No. +31 70 340-3466

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/011953

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-23	as originally filed
Claims, Numbers	
1-18	received on 09.12.2005 with letter of 08.12.2005
Drawings, Sheets	
1/12-12/12	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☒ the claims, Nos. 19-33
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/011953

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-18 in part

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-18 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/011953

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-11,15,18
	No:	Claims	1-5,12-14,16,17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Claims 14-18 encompass a genus of compounds defined only by their function: "a targeting moiety" (claims 14, 17); "other intercalators", "derivatives", "analogues" (claims 15, 18) wherein the relationship between the structural features of the members of the genus and said function have not been defined.
In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (**other than those that might be particularly disclosed in an application**) would fall within the scope of what is claimed.
It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.
Therefore, the claims 14-18 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Moreover, claims 1-18 relate to compounds defined by reference to vague characteristics or properties, namely: "monodentate ligand", "bidentate ligand" (claim 1); "aromatic heterocycles", "thioethers", "isocyanides" (claim 2); "organic molecules having one of this group as an integral part" (claim 4); "organic molecules containing a thioether functionality as an integral part of it" (claim 7); "an amino acid" (claim 8); "an anionic amino acid" (claim 9); "a non-natural alfa or beta amino acid" (claim 10).
In fact, the claims contain so many options, variables and possible permutations that a lack of clarity within the meaning of Article 6 PCT arises.

The claims cover all compounds having these characteristics or properties, whereas the

application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Support is only to be found in the present application for those parts relating to the compounds effectively disclosed in the examples and those specifically mentioned by chemical name in claims 3, 4, 6, 7, 11, 13, 15, 16, 18.

No opinion will be formulated in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT)

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D) are referred to in this communication:

D1 : ZOBI, F. ET AL: INORG. CHEM, vol. 42, 4 May 2003 (2003-05-04), pages 2818-2820, XP008051339.

D2 : ZHANG J ET AL: JOURNAL OF ORGANOMETALLIC CHEMISTRY, ELSEVIER-SEQUOIA S.A. LAUSANNE, CH, vol. 650, no. 1-2, 1 May 2002 (2002-05-01), pages 123-132, XP004351213.

D3 : ALBERTO R ET AL: COORDINATION CHEMISTRY REVIEWS, ELSEVIER SCIENCE, AMSTERDAM, NL, vol. 190-192, 1999, pages 901-919, XP001074720

D4 : PIETZSCH H-J ET AL: BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 11, 2000, pages 414-424, XP001119310

D5 : WO 02/087633 A (BEIJING NORMAL UNIVERSITY) 7 November 2002 (2002-11-07)

D6 : BELLA LA R ET AL: BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 13, no. 3, 15 May 2002 (2002-05-15), pages 599-604, XP002218739.

Novelty (Art 33 (2) PCT)

The subject-matter of claims 1-5, 12-14, 16, 17 is not new in the sense of Article 33(2) PCT. The reasons therefore are the following:

D1 discloses the structure and basic kinetic data of [M(9MeG)2(CH3OH)(CO)3]+ (M= 99TC, Re). These complexes with 99Tc and 188Re are potential cytotoxic agents affecting DNA like cisplatin and could be used as novel radiodiagnostic or therapeutic agents (see page 2818, col. 2, paragraph 1; page 2820, col. 2, paragraph 2; figure 1).
Consequently the subject matter of claims 1, 2, 4, 5, 12, 13, 16 is not new over D1.

D2 discloses Tricarbonylrhenium(I) complexes of bidentate phosphine-derivatized amines (aniline), amino acid (glycine) and a model peptide (glycylglycine). Cytotoxic activity against leukemia, lymphoma, lung, ovary, breast, prostate, liver, illeum tumors, glioma, osteosarcoma, melanoma (see page 130, col. 2; table 4; conclusions).
Therefore rendering the subject matter of present claims 1-3, 12-14, 16, 17 not novel.

D3 discloses the chemistry of [M(OH2)3(CO)3] and formation of imidazole and bidentate pyridine-hydrazone complexes for radiopharmaceutical application (see page 909; page 914). Consequently the subject matter of present claim 16 is not new over D3.

D4 discloses Technetium(I) and Rhenium(I) tricarbonyl complexes with dithioether ligands serving as linkers for coupling the Tc(CO)3 and Re(CO)3 moieties to biologically active molecules. Exemplified for gluthatione (GSH) peptide (see conclusions; page 422, col. 1; figure 4).
Consequently the subject matter of claims 16, 17 is not new over D4.

Inventive step (Art 33(3) PCT)

Should the applicant overcome the above raised objections, an inventive step has to be demonstrated for the subject matter of present claims 1-18 (Art 33(3) PCT).

According to the description (page 2, lines 1-8), the problem underlying the present invention is the non-specificity, the relatively large amounts to be administered as well as the development of resistance to the drug and the impossibility of derivatization with a targeting agent of metal ion coordinated drug in particular of the drug cisplatin.

As solution to this problem, metal complexes that are capable of binding to DNA bases in a fashion similar to cisplatin, in particular complexes consisting on metal tricarbonyl compounds of the general formula as depicted in claim 1 are proposed.

Previously discussed document D1, which can be considered the closest prior art, discloses [M(9MeG)2(CH3OH)(CO)3]+ (M= 99TC, Re) embraced under formulas of claim 1. These complexes with 99Tc and 188Re are potential cytotoxic agents affecting DNA like cisplatin and could be used as novel radiodiagnostic or therapeutic agents containing a radioactive carbon atom.

The difference between D1 and the subject matter of the present application is fact the particular use of alternative ligands in the tricarbonyl complexes as listed by present claims 3, 6-11 or the targeting moieties listed by present claims 15, 18 is not explicitly disclosed by this document D1.

Previously discussed document D4 discloses Technetium(I) and Rhenium(I) tricarbonyl complexes with dithioether ligands.

D5 discloses tricarbonyl coordination complexes having the formula [M(CO)3(MIBI)x(OH2)3-x]+ wherein M is Mn, 99mTc, 186Re or 188Re and MIBI is the etherisonitrile 2-ethoxy isobutylsonitrile

Both documents D4, D5 describe structural modifications in the tricarbonyl coordination compound and therefore render obvious such structural modification of a ligand as claimed in present claims 6, 7.

Therefore the skilled person would have easily contemplated the use of these tricarbonyl complexes of D4 and D5 as alternative tricarbonyl complexes with for the treatment of cancer only relying on known properties of known compounds as reinforced by D1 wherein it is stated "the mechanism of toxicity by coordination to N7 in purine bases in a fashion similar to cisplatin is anticipated to be a possible mode of action for tricarbonylrhenium complexes" (see page 2818, col. 1; paragraph 2)

Consequently an inventive step for the subject matter of present claims 6, 7 cannot be

acknowledged.

D6 describes [99m]Tc(I)-tricarbonyl postlabelled bombesin analogue as tumor imaging agent. The labelling approach of small peptides under mild conditions indicates also the potential application using the rhenium isotopes Re-186/188 (see conclusion; abstract; figure 1)

Consequently the particular embodiment of tricarbonyl compounds as depicted in formula of claim 1 wherein X1 and/or X2 and or X3 are coupled to a targeting moiety consisting of bombesin, as claimed by present claims 15, 18 is also rendered obvious by this document D6.

Furthermore, the attention of the applicant is also drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step.
When the inventive step is solely based on the achievement of a technical effect, such as the chemotoxic and/or radiotherapeutic activity, substantially all embodiments of independent claim 1 (I. e. any tricarbonyl compound embraced under formula as depicted) should exhibit this effect.

However, it is evident that the number of compounds comprising groups encompassed under "a targeting moiety" (claims 14, 17); "other intercalators", "derivatives", "analogues" (claims 15, 18) is such that it is unlikely that all of them posses the effect claimed.

Therefore, as part of the subject matter of claims 1-18 does not exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Consequently an inventive step for the subject matter of claims 1-18 cannot be acknowledged.

Re Item VI
Certain documents cited

Certain published documents

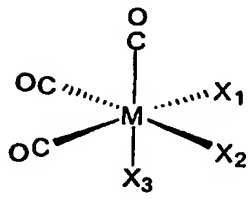
Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/022105	18/03/2004	02/09/2003	02/09/2002
WO2004/097406	11/11/2004	29/04/2004	29/04/2003

The PCT application WO2004/022105 published on 18/03/2004 claims the priority date of 02/09/2002. This earlier application shows: Bidentate ligands including N,N' dimethylethylenediamine for preparation of M(CO)3- tricarbonyl complexes (see example 10; table 1, compound 13)
Thus, it would be prejudicial to the novelty of the subject-matter of claims 16, 17 of the present application.

The PCT application WO2004/097406 published on 11/11/2004 claims the priority date of 29/04/2003. This earlier application shows: Protected l-histidine for coupling to biomolecules and efficient labelling with [M(OH2)3(CO)3]+ by FAC coordination. Histidine derivatives include bidentate ligand. Suitable biomolecules for labelling include bombesin, somatostatin, neurotensin (see page 7, lines 15-20; page 13; examples 4, 6; claims 20, 21)
Thus, it would be prejudicial to the novelty of the subject-matter of claims 16-18 of the present application.

NEW CLAIMS

1. Use of metal tricarbonyl compounds of the general formula:



wherein

M is rhenium or technetium or an isotope thereof;
at least two of X_1, X_2 and X_3 are monodentate ligands; or two of X_1, X_2 and X_3 are part of a bidentate ligand and the other one is optionally a monodentate ligand for the preparation of a chemotoxic and optionally radiotherapeutic prodrug for the treatment of cancer.

2. Use as claimed in claim 1, wherein the monodentate ligand is selected from the group consisting of halogens, CO, aromatic heterocycles, thioethers, isocyanides.

3. Use as claimed in claim 2, wherein the halogens are selected from the group consisting of bromo, iodo, fluoro, chloro.

4. Use as claimed in claim 2, wherein the aromatic heterocycles are selected from the group consisting of pyridine, pyrimidine, pyrazine, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole and organic molecules having one of this group as an integral part.

5. Use as claimed in claim 4, wherein the purine is guanine or 9-methyl guanine.

6. Use as claimed in claim 2, wherein the thioethers are selected from the group consisting of linear substituted dialkyl-thioethers or cyclic thioethers such as

tetrahydrothiophen and other organic molecules containing a thioether functionality as an integral part of it.

7. Use as claimed in claim 2, wherein the isocyanides are selected from the group consisting of organic molecules comprising a terminal -NC group coupled to an alkyl chain optionally comprising a functionality such as a -COOH, $-NH_2$, -X, -SH, -OH group.

8. Use as claimed in claim 2, wherein the bidentate ligand is an amino acid or dicarboxylate.

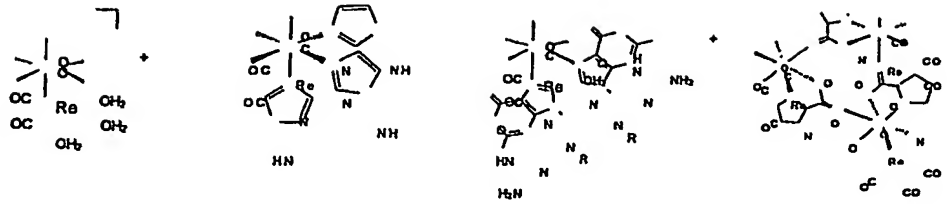
9. Use as claimed in claim 8, wherein the amino acid is an anionic amino acid.

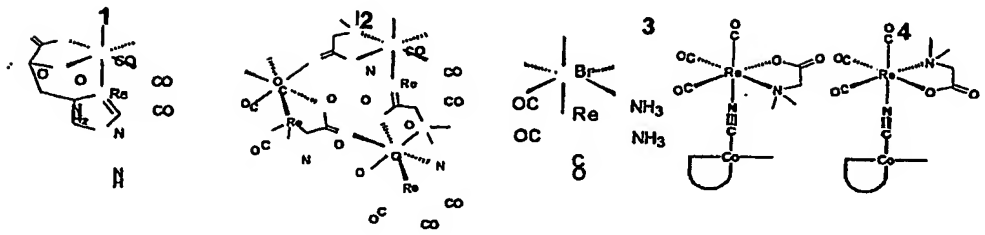
10. Use as claimed in claim 8, wherein the amino acid is a non-natural α- or β-amino acid.

11. Use as claimed in claim 10, wherein the non-natural amino acid is N,N-dimethyl glycine.

12. Use as claimed in any one of the claims 1-11, wherein at least two of the ligands of the tricarbonyl complex shown in formula I are exchanged by guanine or guanosine after 3 days at 37°C with guanine or guanosine being present in a slight excess over rhenium or technetium.

13. Use as claimed in any one of the claims 1-12, wherein the compound is selected from the compounds as depicted hereinbelow





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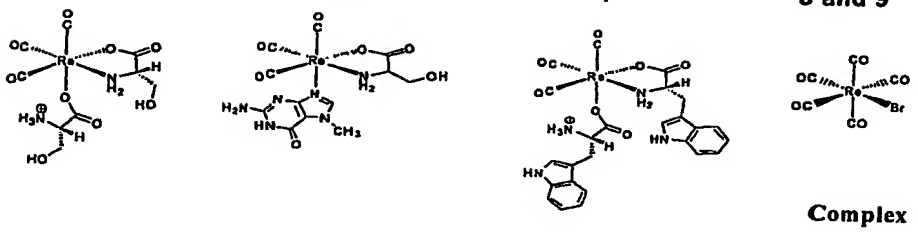

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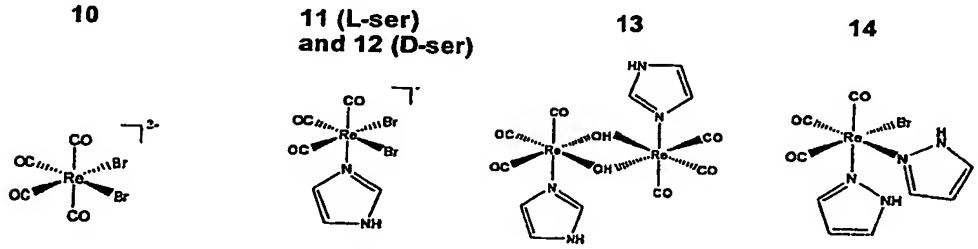
Complex

14



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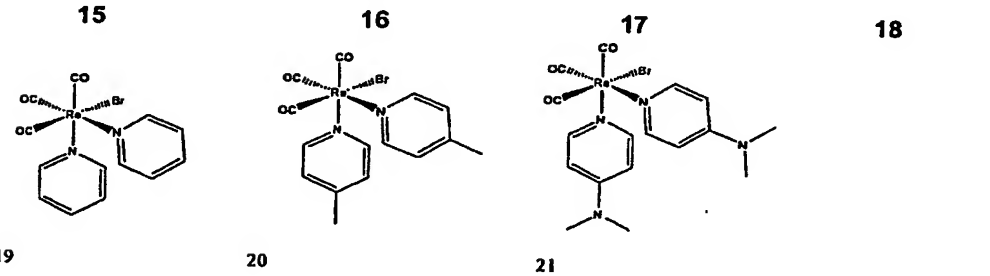

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19 20 21

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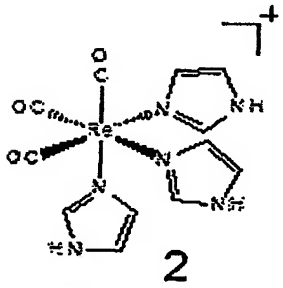
and combinations thereof.

14. Use as claimed in any one of the claims 1-13, wherein X_1 and/or X_2 and/or X_3 are coupled to a targeting moiety.

15. Use as claimed in claim 14, wherein the targeting moiety is selected from the group consisting of bombesin, neurotensin, somatostatin, glucosamine, nucleosides, nuclear localizing sequence peptides (NLS-peptides) oligonucleotides, nucleus targeting molecules such as anthracyclines, acridines and other intercalators, and derivatives or analogues thereof.

16. Compound selected from



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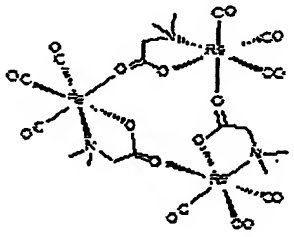

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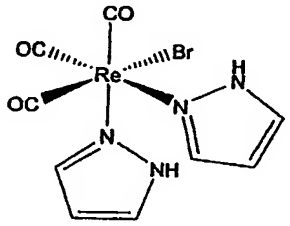

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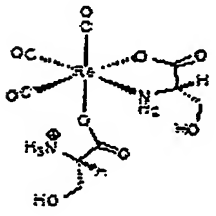

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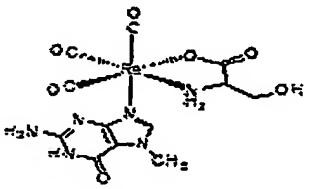
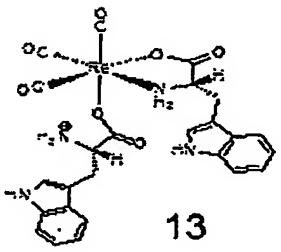


11 (L-Ser)
12 (D-Ser)



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17. Compound as claimed in claim 16, which is coupled to a targeting moiety.

18. Compounds as claimed in claim 17, wherein the targeting moiety is selected from the group consisting of bombesin, neurotensin, somatostatin, glucosamine, nucleosides, nuclear localizing sequence peptides (NLS-peptides) oligonucleotides, nucleus targeting molecules

such as anthracyclines, acridines and other intercalators and derivatives and analogues thereof.